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Rates of glycaemic deterioration in a real-world type 2 diabetes population

Short title: Glycaemic deterioration rates in type 2 diabetes

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AIMS/HYPOTHESIS

There is considerable variability in how diabetes progresses after diagnosis. Progression modelling has largely focused on ‘time to failure’ methods, yet determining a ‘coefficient of failure’ has many advantages. We derived a rate of glycaemic deterioration in type 2 diabetes, using a large real-world patient cohort, and aimed to investigate the clinical, biochemical and immunological parameters associated with fast and slow rates of glycaemic deterioration.

METHODS

We utilised the electronic medical records from patients in the Genetics of Diabetes Audit and Research (GoDARTS) cohort. A model was derived based on a patient’s observed HbA_{1c} measures from first eligible HbA_{1c} after diabetes diagnosis through to study end (defined as insulin initiation, death, leaving area or end of follow-up). Each HbA_{1c} measure was adjusted time-dependently for the effects of non-insulin antidiabetic drugs, changes in BMI and prednisolone use. The presence of LADA was defined as GAD titres >97.5th centile of the population distribution.

RESULTS

The mean glycaemic deterioration for patients with type 2 diabetes and LADA were 0.13(95%CI 0.12,0.14)% and 0.26(0.21,0.32)% HbA_{1c} per year respectively. A younger age of diagnosis and lower HDL were independently associated with higher rates of glycaemic deterioration. The rate of deterioration in those diagnosed over 70 years of age was very low; with 66% having a rate of deterioration less than 0.1% HbA_{1c} per year, and only 1.5% progressing more rapidly than 0.4% HbA_{1c} per year.

CONCLUSIONS/INTERPRETATION

We have developed a novel approach to model diabetes progression in observational data across multiple drug combinations. This approach highlights how glycaemic deterioration in those diagnosed over 70 years of age is minimal supporting a stratified approach to diabetes management.

INTRODUCTION

Type 2 diabetes (T2DM) is a progressive disease, primarily characterised by beta cell failure [1, 2]. This progression is manifested clinically by HbA_{1c} deterioration over time, despite lifestyle and increased pharmacologic intervention. However, the rate at which diabetes progresses is highly variable between patients. Some patients have a rapid deterioration and advance to insulin therapy quickly whilst others can be adequately treated with non-insulin antidiabetic medication in excess of 20 years. Gaining insight into why some patients progress rapidly and some do not will enable a more stratified approach to the management of T2DM by identifying patient subgroups who may require different management depending on their likelihood of diabetes progression.

Previous studies have investigated factors associated with the rate of diabetes progression. However, these studies have only reported an outcome based on progression to antidiabetic medications (i.e., time to initiation of non-insulin antidiabetic medication, failure of monotherapy or time to insulin) [1, 3-9]. In these studies, younger age at diagnosis and insufficient beta cell function were consistently associated with faster diabetes progression. UKPDS reported that presence of positive GAD antibody concentrations predicted an increased likelihood of insulin requirement [3]. Other less well established associations were female sex, low BMI (defined as less than 30kg/m²), weight gain, lower HDL and higher serum creatinine. In addition, we have previously reported that risk of progression, as defined by requirement of insulin treatment, is associated with normal weight or obesity (U-shaped relationship), and higher triglyceride and lower HDL levels [6].

The studies outlined rely on defining an endpoint, such as a glycaemic threshold, or starting a new drug. These 'time to failure' approaches are problematic, particularly in the real-world where decisions to start a drug are subject to prescriber or patient inertia, and where fluctuations

in HbA_{1c}, e.g. due to lifestyle change, can trigger a failure event. A ‘coefficient of failure’ measure was proposed to avoid these difficulties – in essence, deriving a rate of glycaemic deterioration for each patient [10]. This approach was applied to the UKPDS study, reporting a coefficient of failure of 0.34% (3.7mmol/mol) per year with chlorpropamide treatment [10], and to the ADOPT study where a rate of glycaemic deterioration of 0.14% (1.5mmol/mol) HbA_{1c} per year in the metformin monotherapy arm was described [11]. However, to our knowledge, no studies are reported describing the coefficient of failure in settings outwith these clinical trials of monotherapy. Determining rates of deterioration in a population over time is challenging as underlying disease severity reflects not only observed HbA_{1c}, but also lifestyle and pharmacologic interventions.

The aim of this study was to derive a model for the rate of deterioration of T2DM (coefficient of failure) in a large population-based cohort and to investigate the clinical, biochemical and immunological characteristics associated with fast and slow rates of glycaemic deterioration.

METHODS

An observational cohort study was performed using comprehensive electronic medical records from patients in the Genetics of Diabetes Audit and Research (GoDARTS) database, which has been described previously [12, 13]. In short, this contains detailed information on all encashed prescriptions from 1994 onwards in Tayside, Scotland, as well as all biochemistry and BMI measures. So, for each patient we have a comprehensive longitudinal record of diabetes therapy and glycaemic control.

The GoDARTS study was approved by the Tayside Committee on Medical Research Ethics, and informed consent was obtained from all patients (REC reference 053/04).

The GoDARTS cohort and the research question outlined here were studied as part of the Diabetes Research on Patient Stratification (DIRECT) study, an EU FP7 Innovative Medicines Initiative (see www.direct-diabetes.org) project.

Study Population

Diabetes diagnosis was defined as date of first HbA_{1c} $\geq 6.5\%$ (48mmol/mol) (based on the recommended cut-off point for diagnosing diabetes) or first prescription for antidiabetic medication, following a clinical diagnosis of T2DM. Patients were followed from diagnosis until insulin initiation, death, leaving the area or end of follow-up (30th September 2015), whichever came first. To ensure sufficient prescribing information and longitudinal HbA_{1c} and BMI measurements, patients had to have been diagnosed with diabetes on or after 1st January 1994 to be eligible for the study. Patients who progressed to insulin within one year of diagnosis were excluded from the current analysis to minimise inclusion of patients with type 1 diabetes.

GAD antibodies

GAD antibodies were measured at the time of recruitment into GoDARTS, allowing us to define a subgroup of patients who were ‘GADA positive’ (defined as ≥ 11 U/L (97.5th centile)) with latent autoimmune diabetes in adults (LADA), whom we would expect to have a more rapid diabetes progression, with different clinical covariates associated with progression compared to patients with T2DM [3].

Study criteria:

The underlying assumption of our progression model is that change in HbA_{1c} over time is linear, and this is supported by the Belfast Diet Study which reported two linear phases pre and post diagnosis of diabetes [1]. Some patients who had a high HbA_{1c} at diagnosis and subsequent marked improvement in HbA_{1c}, reflecting likely glucose toxicity at presentation, did not fulfil this assumption of linearity. Therefore for all patients we restricted the starting HbA_{1c} value to an upper limit of 8% (64 mmol/mol), and allowed one year from diagnosis to reach this target HbA_{1c} level.

The first HbA_{1c} measure satisfying the inclusion criteria was defined as the study start for that patient. Two subsequent HbA_{1c} measurements were required for a patient to be included in the analysis. In addition, patients were required to have a BMI measurement at diagnosis (defined as the average value +/- one year from diabetes diagnosis) and at least two subsequent BMI measures during the follow-up period. A small number of patients were also excluded during the analysis as they had fewer than three HbA_{1c} and/or BMI measures after outlying data points were removed (described later).

Outcome:

A model was derived for each patient's glycaemic deterioration rate based on observed HbA_{1c} measures from the first eligible HbA_{1c} through to study end.

HbA_{1c} measures were adjusted time-dependently for:

1. Non-insulin antidiabetic drugs: untreated measures were the reference group, defined as measures prior to antidiabetic drug initiation. As metformin was the most commonly prescribed antidiabetic drug and we expected to observe a dose-dependent relationship with HbA_{1c} [14], we divided daily dose into five groups (<1g, ≥1g to <1.5g, ≥1.5g to <2g, 2g, and >2g). The other antidiabetic drugs were grouped solely by drug class either because there was no evidence of a dose-dependent relationship with HbA_{1c} (as is the case for sulphonylureas) or the limited number of measures would result in multiple, small groups (as is the case for thiazolidinediones, acarbose, glucagon-like peptide agonists, dipeptidyl peptidase-4 inhibitors, glinides and SGLT2 inhibitors). Antidiabetic drugs were further grouped into monotherapy, and combinations of dual and triple therapy.
2. BMI change: expressed as percentage change from BMI at diagnosis and categorised as: no change (reference group), any weight gain, and weight loss divided into five groups (<2.5%, 2.5 to 5%, 5 to 7.5%, 7.5 to 10%, and >10%).
3. Glucocorticoid use: a widely recognised side effect of glucocorticoids is to raise HbA_{1c} temporarily [15], and as a significant proportion of patients were prescribed prednisolone during the study period, we adjusted HbA_{1c} measures accordingly (categorised as 'yes' or 'no').

Covariates:

The following covariates were included in the model: age at diabetes diagnosis, gender, and a variable indicating presence of glucose toxicity at diagnosis (i.e. initial HbA_{1c}>8% (64mmol/mol)). BMI, HDL and triglycerides were also included, defined as the average of all measures +/- one year from diagnosis.

Statistical Analysis:

A linear mixed effects model was fitted. As the time intervals between HbA_{1c} measurements are more or less unique to each patient, the 'continuous time/continuous space' spatial data covariance structure provided within the PROC MIXED procedure in SAS was utilised to describe the covariance structure among the errors.

We began by fitting a model with both fixed and random intercept and slope, and adjustment for non-insulin antidiabetic drugs, prednisolone use and changes in BMI over time, fitted as fixed effects. The studentised residuals were examined and any HbA_{1c} measures more than three standard deviations from the mean were removed as these values were considered likely outliers for that patient.

We then ran the model again for T2DM and LADA patients separately and compared the individual patient glycaemic deterioration rates. These were calculated by adding together each patient's random slope with the population average (fixed) slope.

The model was then expanded in T2DM patients only, due to small numbers in the LADA group, to include the baseline clinical covariates of interest. To model the effect of each covariate on glycaemic deterioration, an interaction term between the covariate and time was included. We fitted univariate models in which baseline covariates were added singly, and a multivariate model that included all univariately significant covariates together. Age at diagnosis was split into four age bands (<50, 50 to 60, 60 to 70 and >70 years), BMI was split

into five categories based on WHO definitions (<25, 25 to 30, 30 to 35, 35 to 40 and >40 kg/m²). HDL and triglycerides were split into four clinically meaningful bands (HDL: <1, 1 to 1.2, 1.2 to 1.4 and >4; triglycerides: <1.5, 1.5 to 2.5, 2.5 to 3.5, and >3.5 mmol/L), with an additional 'missing' group created to avoid excluding patients with missing values from the multivariate model.

All analyses were performed using SAS 9.4 and $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Patient characteristics

From a total of 6531 patients who did not progress to insulin within one year of diagnosis, 5488 (84%) met the study inclusion criteria. A detailed flow chart of the study population derivation is presented in supplementary figure 1. The median (IQR) study follow up time was 9.4(6.2,12.4) years and the median (IQR) number of HbA_{1c} and BMI measures per patient was 21(14,29) and 20(13,29) respectively. A total of 121,926 HbA_{1c} measures were generated in the 5488 patients. A comparison of characteristics of patients included and excluded in the study is presented in supplementary table 1. Patients excluded from the study were younger, with higher BMI, lower HDL, higher triglycerides and higher HbA_{1c} at diagnosis. In addition, there were higher proportions of patients with LADA and/or who had progressed to insulin therapy by the end of the study period. As expected LADA patients were diagnosed younger with a lower BMI than patients with T2DM.

Linear mixed model derived effects

The linear mixed model included 112 different drug combinations as fixed effects. These represent the model derived estimates for HbA_{1c} reduction by a particular drug combination compared to no treatment. The drug effects for the most commonly prescribed combinations (defined as more than 500 measures) are presented in supplementary table 2. There was a total of 28,309(23.2%) untreated measures from 3736(68%) patients. We observed a dose-dependent relationship with metformin with less than 1 gram per day lowering HbA_{1c} by 0.07(0.03,0.11)% (0.80(0.3,1.2)mmol/mol) and more than 2 grams lowering HbA_{1c} by 0.50(0.46,0.55)% (5.5(5.0,6.0)mmol/mol) on average. A total of 4557(4%) of HbA_{1c} measures were whilst on prednisolone. The effect of prednisolone was to increase HbA_{1c} by 0.30(0.27,0.33)% (3.3(3.0,3.6)mmol/mol) on average (data not shown).

The BMI effects derived from the model are presented in supplementary table 3. The coefficient presented is the effect of BMI change from baseline on HbA_{1c} with no change as the reference group. For example, the effect of a 10% BMI reduction was to reduce HbA_{1c} by 0.40(0.36,0.43)% (4.4(3.9,4.7)mmol/mol) on average.

Rates of glycaemic deterioration in T2DM and LADA

The model derived patient glycaemic deterioration rate is the rate of change of HbA_{1c} per year after adjusting for the effect of drug treatment and BMI change. The distribution of the patients' glycaemic deterioration rate is presented in figure 1, with patients with T2DM (n=5342) and LADA (n=146) presented separately. The mean (95% CI) coefficient of failure for patients with T2DM was 0.13(0.12,0.14)% (1.4(1.3,1.5)mmol/mol) per year. By comparison, the coefficient of failure for patients with LADA was approximately twice as rapid at 0.26(0.21,0.32)% (2.8(2.3,3.5)mmol/mol) per year.

Clinical characteristics associated with glycaemic deterioration in T2DM

To investigate what clinical covariates other than GADA positivity are associated with glycaemic deterioration, we expanded the model to include interaction terms between baseline clinical covariates and time within the T2DM group. The results for the overall model are presented in table 1. In the univariate analyses, younger age, male gender, glucose toxicity at presentation, higher BMI, lower HDL and higher triglycerides were all associated with higher rate of glycaemic deterioration. However, in the multivariate model, only younger age at diagnosis and lower HDL were independently associated with higher rate of glycaemic deterioration: Patients diagnosed younger than 50 deteriorated 0.15(0.13,0.17)% (1.6(1.4,1.9)mmol/mol) HbA_{1c} per year faster than patients diagnosed over 70; and patients with an HDL less than 1mmol/L deteriorated 0.03(0.01,0.04)% (0.3(0.1,0.4)mmol/mol) per year faster than patients with an HDL greater than 1.4mmol/L. The lack of independent

association of BMI, higher triglycerides and glucose toxicity with rate of glycaemic deterioration in the multivariate model is likely due to the fact that these variables are all highly correlated, as seen in table 2. Young patients (diagnosed under 50) are significantly more obese, with higher baseline HbA1c and triglycerides than older patients (diagnosed over 70).

To further investigate the relationship between younger age at diagnosis and higher rates of glycaemic deterioration, the mean (95% CI) coefficient of failure grouped by five-year age bands for patients with T2DM is presented in figure 2. Of the patients diagnosed under 50, 15% had a glycaemic deterioration rate of greater than 0.4% (4.4mmol/mol) per year, compared with 1.5% of the patients diagnosed over 70. Conversely 66% of the patients diagnosed over 70 had a glycaemic deterioration rate less than 0.1% (1.1mmol/mol) per year compared with just 24% of the patients diagnosed under 50.

DISCUSSION

In this large, observational, population-based study with a maximum follow-up period of over 20 years, we have applied a novel approach to modelling diabetes progression. We have shown that in a real-world setting the underlying mean coefficient of failure (rate of glycaemic deterioration) in patients with T2DM is 0.13(0.12,0.14)% (1.4(1.3,1.5)mmol/mol) HbA_{1c} per year and in patients with LADA it is faster, with a mean rate of 0.26(0.21,0.32)% (2.8(2.3,2.5)mmol/mol) HbA_{1c} per year. Furthermore, our results suggest that patients with T2DM who deteriorate the fastest are those diagnosed under 50 years old and there is very limited deterioration in those diagnosed over the age of 70.

We report a coefficient of failure in patients with T2DM comparable to that of the ADOPT clinical trial, which reported a 0.14% (1.5mmol/mol) annual rate of deterioration in HbA_{1c} in a metformin monotherapy cohort [11]. Moreover, we know from UKPDS that GADA positivity is a strong predictor of diabetes progression [3], and here we have shown that patients with LADA progress approximately two times faster than patients with T2DM.

Our findings are in accordance with other studies that reported the association between younger age at diagnosis and faster progression of diabetes [1, 4-8]. Patients diagnosed younger than 50 progress rapidly compared with patients diagnosed over the age of 70 (figure 2), suggesting patients diagnosed younger may benefit from being treated more aggressively with earlier initiation of antidiabetic medications, particularly if future therapies can be established to delay progression. Conversely, diabetes diagnosed in a high proportion of older people progresses at a negligible rate and this is consistent with the need for less aggressive treatment targets in these patients. The finding that in the real-world, 66% of patients with T2DM diagnosed after the age of 70 progress at a rate less than 0.1% (1.1mmol/mol) per year, and that only 1.5% progress at a rate more than 0.4% (4.4mmol/mol) per year is striking and highlights how

glycaemic monitoring and management in those diagnosed over 70 years does not need to be so aggressive as those diagnosed under 50 years of age.

Low HDL is commonly observed in patients with T2DM and has been previously shown to be associated with progression of diabetes [6, 9]. In this study we replicate those findings: in the overall, multivariate model, apart from younger age at diagnosis, lower HDL is the only other independent predictor of progression in patients with T2DM.

The aim of this study was to derive a ‘rate of deterioration’ or ‘coefficient of failure’, which we believe has many advantages over a time to failure model. However there are a number of assumptions made and requirements of the data in order to develop this model. Firstly we assume a linear deterioration in HbA_{1c} . This is supported by the Belfast Diet Study which reported two linear phases pre and post diagnosis of diabetes [1], however, there may be patients who do not follow this linear decline who are not well accounted for in our model. Secondly, the patients who do not make it into the model largely do so because they have a high HbA_{1c} at diagnosis that does not fall below 8% within the first year, a requirement for inclusion in our model, or because they have too few HbA_{1c} measures before they progress onto insulin. As such our model excludes those with the most aggressive disease and/or those who present late with a high HbA_{1c} , and focuses on those diagnosed close to diabetes onset or with less aggressive disease. As such our coefficients of failure are likely to under-estimate the true progression rate in the population. Thirdly the fact that we are studying real world clinical patients means that we lack some key measures that may be important for glycaemic deterioration, such as measures of beta-cell function and insulin resistance.

In summary, we have developed a novel approach to model the coefficient of failure in observational data across multiple drug combinations. This approach can be used to investigate biological determinants of progression as well as the impact of different diabetes and non-

diabetes drugs on glycaemic deterioration. We confirm that GADA are associated with greater glycaemic deterioration, and for the first time quantify the rate of glycaemic deterioration in the elderly. Our findings of minimal glycaemic deterioration in this elderly onset group has important implications for stratifying diabetes care, suggesting less intensive glycaemic monitoring and management is required for this patient group.

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DUALITY OF INTEREST

PF is a member of advisory boards for Sanofi Aventis and Eli Lilly and has received research funding from Sanofi Aventis, Eli Lilly and Novo Nordisk.

CONTRIBUTION STATEMENT

EP designed the study, interpreted the data and contributed to the writing of the paper. LD did the statistical analysis, interpreted the data and wrote the paper. PF, CJ, KZ and AD contributed to the interpretation of the data, and critically assessed and reviewed the final draft of paper.

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Table 1: Differences in estimated glycaemic deterioration rates in patients with type 2 diabetes

		Univariate Analysis		Multivariate Analysis	
	n	Unadjusted Coefficient (95% CI)*	P-value	Adjusted Coefficient (95% CI)**	P-value
Age (years):					
<50	1430	0.16(0.15 to 0.18)	<0.0001	0.15(0.13 to 0.17)	<0.0001
50-60	1820	0.08(0.07 to 0.10)	<0.0001	0.08(0.06 to 0.09)	<0.0001
60-70	1269	0.04(0.02 to 0.05)	<0.0001	0.03(0.02 to 0.05)	<0.0001
>70	823	REF		REF	
Gender:					
Males	3013	0.01(0.001 to 0.02)	0.0289	0.003(-0.01 to 0.01)	0.5221
Females	2329	REF		REF	
Glucose toxicity:					
No	3574	REF		REF	
Yes	1768	0.02(0.01 to 0.03)	0.0019	0.01(-0.003 to 0.02)	0.1508
BMI (kg/m ²):					
<25	533	REF		REF	
25-30	1890	0.01(-0.01 to 0.03)	0.3928	-0.01(-0.02 to 0.01)	0.4969
30-35	1703	0.03(0.01 to 0.05)	0.0030	0.001(-0.02 to 0.02)	0.9224
35-40	774	0.04(0.01 to 0.06)	0.0008	-0.01(-0.03 to 0.01)	0.5388
>40	442	0.08(0.06 to 0.10)	<0.0001	0.02(-0.004 to 0.04)	0.1063
HDL(mmol/L):					
<1	1275	0.06(0.04 to 0.07)	<0.0001	0.03(0.01 to 0.04)	0.0012
1-1.2	1524	0.04(0.02 to 0.05)	<0.0001	0.02(0.005 to 0.03)	0.0099
1.2-1.4	1168	0.01(-0.001 to 0.03)	0.0615	0.003(-0.01 to 0.02)	0.6598
>1.4	1119	REF		REF	
Missing	256	-0.001(-0.02 to 0.02)	0.9266	-0.01(-0.03 to 0.02)	0.4104
Trigs (mmol/L):					
<1.5	790	REF		REF	
1.5-2.5	1391	0.01(-0.01 to 0.02)	0.4238	-0.001(-0.02 to 0.02)	0.9214
2.5-3.5	858	0.02(-0.003 to 0.03)	0.1003	-0.002(-0.02 to 0.02)	0.8434
>3.5	819	0.03(0.02 to 0.05)	0.0003	0.001(-0.02 to 0.02)	0.9482
Missing	1484	-0.003(-0.02 to 0.01)	0.7292	0.005(-0.01 to 0.02)	0.5473

**Units are % HbA_{1c} per year, adjusted only for antidiabetic medication, prednisolone use and BMI change. **Units are % HbA_{1c} per year, adjusted for antidiabetic medication, prednisolone use and BMI change, age at diagnosis, gender, glucose toxicity, BMI, triglycerides and HDL. The values are expressed as the absolute difference in progression rate between the study group and the reference group. Positive values mean that the glycaemic deterioration rate is faster.*

Table 2: Characteristics at diagnosis of patients with type 2 diabetes by age category

	Age at diagnosis (years)				
	<50	50-60	60-70	>70	<i>P</i> ** (<50 vs >70)
N	823	1430	1820	1269	
Males	486(59.1%)	833(58.3%)	1028(56.5%)	666(52.5%)	0.0032
BMI(kg/m ²)	34.6(6.9)	32.7(6.2)	30.9(5.2)	29.1(4.4)	<0.0001
HbA1c(%)	8.2(1.8)	8.1(1.8)	8.0(1.9)	7.8(1.7)	<0.0001
Glucose toxicity	320(38.9%)	509(35.6%)	590(32.4%)	349(27.5%)	<0.0001
HDL(mmol/L)	1.1(0.3)	1.2(0.3)	1.2(0.3)	1.3(0.3)	<0.0001
Triglycerides (mmol/L)*	2.6(1.7-4.0)	2.4(1.7-3.5)	2.3(1.6-3.1)	1.9(1.4-2.7)	<0.0001

*Data are mean(sd) or N(%); * Median(IQR); **Comparison of patients was by t-test for continuous variables (triglycerides were log transformed) and Chi-square for categorical*

FIGURE LEGENDS

Figure 1

Distribution of rate of glycaemic deterioration (increase in adjusted HbA_{1c} per year characterised in % units). Patients with T2DM are represented in purple and LADA patients in green.

Figure 2

Mean (95%) rate of glycaemic deterioration (increase in adjusted HbA_{1c} per year characterised in % units), by age at diagnosis. The number of patients in each age band is represented on the primary y-axis and the glycaemic deterioration rate is represented on the secondary y-axis.